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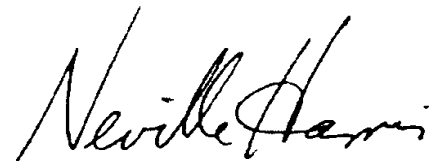
CERTIFICATE

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I hereby certify that annexed is a true copy of the Provisional Specification as filed on 18 April 2000 with an application for Letters Patent number 504057 made by NEW ZEALAND MILK INSTITUTE LIMITED.

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Neville Harris
Commissioner of Patents



TITLE Fortified dietary formulations.

FIELD

The present invention relates to the development and use of a fortified diet for the reduction of the incidence and effects of vascular, particularly cardiovascular disease, at least in cases where raised plasma homocyst(e)ine and verified or unverified diabetes are involved in the aetiology.

BACKGROUND

Diabetes mellitus is a common endocrine disorder that results in substantial morbidity and mortality, and leads to considerable financial costs to individual patients and health care systems. Treatment with either insulin or diet and hypoglycaemic drugs provides palliation of the condition but often cannot prevent the feared vascular complications of the disease such as premature coronary heart disease. Diabetes is the single largest cause of coronary heart disease, and may present with symptoms of the heart disease without any other obvious manifestations of diabetes. Vascular occlusive disease of other organs such as the legs, eyes or brain may also result from diabetes. Diabetes is the single commonest cause of leg gangrene, acquired blindness, and probably stroke in many parts of the world.

These considerations has provided the impetus for intensive research into better methods of preventing these disorders.

Among the newer preventive strategies that have been proposed, removal of environmental triggers of the disorders, and/ or modification of coexistent contributory metabolic conditions

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have received most attention world wide. Identification of environmental triggering factors has focused on possible dietary factors or infections. The modification of vascular disorders associated with the diabetes whether or not diabetes co-exists has also been a major aim of dietary research.

- 25 Recently, the rather tight linkage between raised plasma homocyst(e)ine levels and cardiovascular disease has been recognised and the usefulness of adequate dietary supplies of various B vitamins to reduce these levels has again been highlighted.

The problem to be solved might be expressed as "To reduce the incidence of diabetes-related cardiovascular disease" and this specification will describe solutions involving a set of novel
30 dietary components.

DEFINITIONS

"Vitamin" as used herein refers to one of a set of compounds that are essential for the maintenance of normal metabolic functions of a given organism but which is unable to be synthesised, and so must be furnished from an exogenous source. (Goodman & Gillman). For
35 example, man and guinea pig require ascorbic acid (vitamin C).

The **B group vitamin complex** comprises some of the known water-soluble vitamins, and includes folic acid, hydroxy- or cyano-cobalamine (B12,) and pyridoxine (B6). It appears that they were somewhat arbitrarily grouped together in historical times largely because of common origins in their typical sources; yeast, and liver.

40 OBJECT

It is an object of this invention to provide an improved dietary product for reducing the incidence and severity of diabetes and/or related illnesses, or at least to provide the public with a useful choice.

STATEMENT OF INVENTION

- 45 In a first broad aspect this invention provides a fortified dietary supplement capable of reduction of the incidence and effects of vascular, particularly cardiovascular disease; the fortified dietary supplement comprising a combination of a cow milk or cow milk product having a beta casein content substantially comprised of the A2 variant only or no beta casein at all, together with an effective amount of at least one compound selected from the range of

50 compounds capable of reducing plasma levels of homocyst(e)ine.

A preferred set of "compound or compounds selected from the range of compounds capable of reducing plasma levels of homocyst(e)ine" comprises an effective amount of one or more vitamins selected from the range of B group vitamins.

Preferably the selected vitamins include folic acid, B12, and pyridoxine.

55 Preferably all three are used in the fortified dietary supplement.

Optionally the invention provides a milk as described previously, without added B vitamins, for the purpose of the prevention of both Type 1 and Type 2 diabetes.

In a second broad aspect this invention provides a fortified dietary supplement capable of removing two risk factors associated with diabetes and coronary vascular disease. the fortified
60 dietary supplement comprising a combination of a cow milk or cow milk product substantially free of A1 and B casein, together with an effective amount of vitamins selected from the range of B group vitamins.

Preferably the selected vitamins are folic acid, B12, and pyridoxine.

A preferred range of concentrations of folic acid if comprising the single representative of the
65 B vitamins by an adult human is from 300 to 500 micrograms (mg) intake per day; more preferably 400 micrograms.

Assuming a daily intake of 400 ml of milk, this corresponds to 1 microgram folic acid or the equivalent thereof per ml of milk.

A preferred range of concentrations of vitamin B12 if comprising the single representative of
70 the B vitamins is from 4 to 7 micrograms per day; more preferably 5 micrograms.

Assuming a daily intake of 400 ml of milk, this corresponds to 0.012 mg vitamin B12, or the equivalent thereof per ml of milk.

A preferred range of concentrations of pyridoxine if comprising the single representative of the B vitamins is from 1.5 to 4 mg per day; more preferably 2 mg.

75 Assuming a daily intake of 400 ml of milk, this corresponds to 20 mg pyridoxine (B6) or the equivalent thereof per ml of milk.

A preferred range of concentrations of folic acid in conjunction with vitamin B12 is from 300

to 500 micrograms intake per day. a preferred range of concentrations of vitamin B12 is then from 4 to 7 mg vitamin B12 per day.

- 80 A preferred range of concentrations of folic acid in conjunction with pyridoxine is from 300 to 500 micrograms intake per day, and a preferred range of concentrations of pyridoxine is then from 1.5 to 4 mg per day.

A preferred range of concentrations of pyridoxine in conjunction with vitamin B12 is from 1.5 to 4 mg per day and a preferred range of concentrations of vitamin B12 is then from 4 to 7
85 mg vitamin B12 per day..

A preferred range of concentrations of folic acid in conjunction with vitamin B12 and in conjunction with pyridoxine is from 300 to 500 micrograms intake per day, and a preferred range of concentrations of vitamin B12 is then from 4 to 7 micrograms per day and a preferred range of concentrations of pyridoxine is then from 1.5 to 4 mg per day.

- 90 In a related aspect the invention provides a product composed of B vitamins and A2 casein; the product being capable of improving the status of the cardiovascular system, and of lowering the risk of a diabetic condition being initiated.

At least one further compound capable of reducing plasma levels of homocyst(e)ine is betaine (trimethylglycine), and a preferred daily intake of this compound is up to 1 g per day; more
95 preferably about 100 mg per day, and preferably together with the other specified B vitamins and with a milk having a specified composition of casein.

A method for preparing a fortified milk product as claimed in any previous claim, comprising the steps of selecting a milk having a specified composition of casein as previously described in this section, optionally pasteurising the milk, and then of adding selected B vitamin ingredients
100 to reach a final concentration as previously described in this section

A method for minimising the incidence and/or the effects of the medical condition diabetes mellitus comprising the steps of using, in a diet, an effective amount of a fortified milk product as claimed in any previous claim.

Preferably the fortified milk product replaces any unfortified milk product in the diet.

- 105 A method for minimising the incidence and/or the effects of coronary heart disease comprising the steps of using, in a diet, an effective amount of a fortified milk product as previously described in this section.

A fortified milk product comprising a vitamin-fortified ice cream made from milks of the A2 casein type.

- 110 A fortified milk product comprising a vitamin-fortified yoghurt made from milks of the A2 casein type.

Preferably the fortified milk product replaces a corresponding unfortified milk product in the diet, and more preferably a consumer of a fortified milk product according to this invention will avoid milk products not based on type A2 caseins.

- 115 A method for making a fortified milk product according to this invention including the steps of obtaining a milk or milk product substantially free of type A1 or type B casein, and adding an effective amount of one or more compounds selected from the list of pyridoxine, folic acid, cobalamine, and betaine.

- 120 A method for reducing an incidence of a disease (including cardiovascular disease, diabetes and "other diseases" as defined elsewhere in this specification), in a population, the method including the steps of providing a fortified milk product according to this invention and of making it available to the population.

PREFERRED EMBODIMENT

- 125 The description of the invention to be provided herein is given purely by way of example and is not to be taken in any way as limiting the scope or extent of the invention.

PRINCIPLES:

It is known that:

1. Diabetes tends to cause vascular disease, although the exact mechanism or mechanisms are not clear.
- 130 2. High levels of plasma homocyst(e)ine are linked to vascular disease including cardiovascular disease, and is believed to be a more accurate risk indicator of possible heart disease (occlusive vascular conditions) than cholesterol.
3. A diet including milk including type A1 beta casein or type B beta casein is associated with diabetes, from population statistics.

- 135 4. Deficiencies of the B vitamins folic acid, pyridoxine, and cyanocobalamine (B12) leads to higher plasma homocyst(e)ine. Conversely, high plasma homocyst(e)ine levels can be controlled with additional folic acid, pyridoxine, and cyanocobalamine, and in some cases, also with betaine.
5. There is a close relationship between higher plasma homocyst(e)ine and higher rates of incidence of cardiovascular disease (and for other vascular-based diseases as well)
- 140 6. Partly due to (a) sub-optimal actual dietary levels being common, (b) an underassessment of actual needs (see for example Rimm E B et al JAMA 1998 Feb 4; 279(5): 359-364), (c) common (that is, 10%, 15% of the general population) genetic abnormalities in metabolism of folic acid, a large proportion of humanity is close to a deficient status for folic acid if not actually in a disease state. Folic acid deficiency also leads to a number of other diseases.
- 145 7. In the western world, cardiac problems cause about 45% of deaths.
8. Diabetes has a greater incidence than generally believed; it is not easy to diagnose all cases presented.

Mechanisms of action for (1) and (2) above are not well understood. Nevertheless we believe
 150 that a combined treatment including both strategies will exhibit a synergistic effect on vascular disease, and it should be noted that some recent publications describe measured improvement in blood vessel condition in adults having hyperhomocyst(e)inemia after supplementation of folic acid over some weeks. See for example Woo et al J Am Coll Cardiol 1999 Dec 34 (7);2002-2006 (brachial artery), or Hackam et al Am J Hypertens 2000 Jan; 13 (1 Pt 1) 105-110
 155 (carotid plaques).

Given that both (1) and (2) act on the same target organ (vascular walls), the invention proposes (A) various combinations of milk comprised of predominantly type A2 casein, or derivatives thereof, plus (B) supplements of folic acid, together with B6 and B12 which are known to be mutually supportive even synergistic in their effects on hyperhomocystinemia;
 160 the combination of (A) and (B) being expected to show synergy in relation to beneficial effects on blood vessel walls and the like in patients with known or unsuspected diabetes, and the (B) part of the invention alone being also generally useful in minimising the effects of a number of diseases other than diabetes, some of which are related to blood vessels, especially occlusive cardiovascular diseases, and to other diseases. In such cases the (A) component of the
 165 invention has at least no undesirable effects and may actually reduce the onset of diabetes in at-risk persons. Note that the incidence of "unsuspected diabetes" in patients having vascular

disease is significant. "Other diseases" above includes: prematurity, loss of memory in the elderly, Alzheimer's disease, teratogenic effects; neural tube closure problems resulting in spina bifida and the like, asthma, bowel (colorectal) cancer, cervical cancer and/or endometrial cell dysfunction, and abnormalities in haematopoiesis.

DETAILS:

By "various combinations" of the fortified dietary supplement we propose some examples of acceptable products, for instance:

1. A liquid milk having a type A2 casein composition; substantially lacking either type A1 or type B casein together with added B vitamins, preferably B6, B12, and folic acid or analogues thereof. Preferably all three vitamins are added and a preferred amount is about the same as the accepted human daily requirement, namely about 400 micrograms (μg) folic acid, 5 μg of B12 and 2 mg of B6. Assuming that the average daily intake of milk is 400 mls, this implies a concentration of 100 μg folic acid, 1.25 μg B12, and 0.5 mg B6 per 100 ml of milk having type A2 casein but no type A1 casein.
2. Possibly, the same end result may be obtained by providing a wheat flour supplemented with folic acid or analogues thereof, and milk, separately.
3. A more reliable alternative (in terms of securing the goal of a reliable daily intake) is a fortified breakfast cereal, having additional B vitamins to supply a daily intake as above, sold as a "kit of parts" together with a container of suitably preserved A2-casein milk. This may comprise an amount of "UHT" or otherwise long-life milk in a sachet, and the combination might be sold or dispensed as single "ready-to-use" breakfast amounts of cereal and corresponding milk.
4. Vitamin-fortified ice creams made from milks of the A2 casein type.
5. Infant milk, suitable for even very young infants, possibly fortified with vitamins to a lesser extent and made from milks of the A2 casein type.
6. Milk designed for acceptability by young people, fortified with vitamins and made from milks of the A2 casein type. (Young women are at risk of becoming pregnant, and there are reports of atheromatous lesions in young American soldiers during the Vietnam war.

- 195 7. Any one of the entire range of edible milk-based products such as milk powder, milk chocolate, cheese, and the like, fortified with vitamins and made from milks of the A2 casein type. (This may be less applicable to butter).

Water, then wheat flour, then milk seem to be the three most predictable components of the average Western diets. Cereals are very often the "standard breakfast. Hence we select those
200 components so that an adequate daily intake is achieved without special effort - the need to remember to take pills or the like. Most probably the various products suggested in this specification would be offered for sale as "heart-friendly" or the like alternatives.

Heat stability of natural folic acid is poor, but artificial folates or combinations will tolerate pasteurisation for example with minimal loss. Light stability of B12 in milk is poor, hence any
205 product according to the invention should preferably be stored away from sunlight.

The rationale for this preventive treatment approach is a combination of removal of a dietary factor found in cow milk and implicated in both diabetes and coronary heart disease, and fortification of milk or milk products rendered free of the adverse dietary factor, with a combination of B group vitamins and/or betaine, which are capable of lowering plasma
210 homocyst(e)ine levels. Methods of producing the individual properties of such a milk and products are known to those familiar with the art, but the combination of such properties with the intention of preventing occlusive vascular disease is unique to this invention.

Elevated levels of homocyst(e)ine are associated with increased risk of coronary and other vascular occlusive disease, whether or not associated with diabetes.

215 **EXAMPLE 1:**

In a first aspect the invention relates to prevention of diabetes, both Type 1 and Type 2, by provision of cow milk or milk products which are substantially free of proteins which are capable of yielding beta-casomorphin-7 or other longer peptides containing the beta-casomorphin-7 sequence, after intestinal digestion in the recipient mammal (including man).

220 This may be accomplished by

- a) selection of cows which yield beta casein only of the A2 variety to provide the milk-such milk not yielding the beta-casomorphin-7 or related peptides after intestinal digestion
- b) (optionally) removal of all or substantially all beta-caseins from milk by physical, chemical or enzymatic means

- 225 c) (optionally) genetically altering the milk source cows such that the beta-caseins which yield beta-casomorphin-7 or related peptides do not occur after digestion. Such genetic alteration may totally remove the required gene sequence for the either the specific, or all, beta casein.

230 Preferably the selection of the cows producing the required milk are identified by measurement of the various beta caseins in their milk and using only those milks containing A2 beta-casein.

Preferably the beta casein variants are identified by gel electrophoresis or other method familiar to those skilled in the art.

235 Optionally the selection of the cows may be carried out by identification of the variant beta casein genes found in blood, milk or other tissues of the cows, by methods familiar to those skilled in the art.

EXAMPLE 2:

In the second aspect the invention consists of fortifying the milk containing the preferred beta-casein composition as described above with a combination of B group vitamins which can
240 lower the blood levels of homocyst(e)ine whether or not diabetes or other conditions coexist.

Preferably the fortifying vitamins include

- a) folic acid in an amount shown to lower plasma homocyst(e)ine levels when administered in foods.

245 Such amounts consist of at least 100 micrograms found in the usual daily amount of milk consumed, and preferably less than 280 micrograms in such an amount.

b) cobalamine (vitamin B12) -preferably as hydroxy-cobalamine but optionally cyano-cobalamine in amounts preferably equalling the average daily requirement (5 micrograms) in the usual amount of milk consumed/day, but not exceeding twice this amount This amount will prevent any adverse effects of folic acid given in the above doses to individuals
250 who may be deficient in B12. Additionally such an addition may enhance the homocyst(e)ine lowering effects of folic acid

c) pyridoxine -preferably as the hydrochloride in amounts equalling the average daily requirement (10 mg) in the usual amount of milk consumed/day, but not more than twice

255 this amount. Such an addition may enhance the lowering of blood levels of homocyst(e)ine under certain conditions.

260 Preferably such vitamin fortifications are added by mensurated line feeder methods familiar to those skilled in the art, prior to making the milk available for consumption or further manufacture into milk products. Preferably such milk /milk products are analysed for verification of the vitamin additions prior to being consumed by methods familiar to those skilled in the art.

The liquid milk thus fortified may be of any of the commercial presentations of the milk including fat reduced milk, ultra heat treated milk or pasteurised milk. It may also include yoghurt, ice cream, or other milk products.

Preferably the milk is presented in opaque containers to preserve the B12 content.

265 THEORY OF OPERATION:

We believe that the invention may be in part explained by discoveries described in the following scientific publications from the inventor and others.

Part 1: The nature of a dietary environmental agent which can trigger diabetes.

270 Previous research has shown an epidemiological association between the quantity of consumption of liquid milk and Type 1 diabetes (Scott et al), and that the probable cause of this association can be further apportioned to the A1 and B beta casein moieties of the milk (Elliott et al 1998). Other milk proteins are not associated with diabetes, in particular the A2 variant of beta casein appears to be harmless. Others research has shown an association between Type 1 diabetes and high levels of antibodies to A1, but not A2 beta-casein - at least 275 in some populations (Elliott et al 1999).

280 Virtanen et al (1999) have shown that children who develop diabetes drink more cow milk than those who do not when the genetic predisposition to diabetes is taken into account. Infants born with a genetic predisposition to diabetes and fed a diet containing no cow milk in infancy are less likely to develop early signs of disease affecting the insulin producing cells of the body than those fed cow milk (Akerblom et al 1999)

Bennet et al have shown an association with the early childhood consumption of cow milk and Type 2 diabetes.

Thus in humans it appears that milk consumption may be an environmental trigger to both types of diabetes and at least in Type 1 diabetes this appears to be associated with the content of A1 and B beta caseins of the milk-but not the A2 beta casein content.

Both A1 and B beta caseins yield beta-casomorphin-7 after digestion by intestinal digestive enzymes, whereas A2 beta casein does not (Erhard et al). Beta casomorphin-7 has opiate type effects on intestinal transit time in animals (including humans) and also has immunosuppressive activity on human intestinal lymphocytes (Elitsur et al). Such opiate like effects may exacerbate a genetic predisposition to Type 1 and Type 2 diabetes.

Part 2: The association of coronary heart disease with diabetes

Both Type 1 and Type 2 diabetes increase the risk of coronary heart disease 5-10 fold.

In some communities Type 2 diabetes occurs in greater than 10% of the adult population over the age of 40, and in these communities diabetes is the leading cause of coronary heart disease. Type 1 diabetes has a smaller contribution to the population coronary heart disease rate. Diabetes incidence of both types is increasing dramatically throughout the world. (WHO 1998).

Part 3: The association of coronary heart disease with the consumption of liquid milk and in particular milks containing the A1 and B variants of beta casein.

Several epidemiological studies have shown an association between the consumption of liquid milk and coronary heart disease mortality rates and this appears to be due to the protein content of the milk rather than the fat content.

As can be anticipated given the association of diabetes with heart disease, the consumption of A1 beta casein appears to be better associated with coronary heart disease mortality rates than is any other constituent of the cow milk.

Part 4: Is there a link between hyperhomocyst(e)inemia and diabetes?

Very recently, Hoogveen et al in *Circulation* 2000 4;101(13):1506-11 reported that hyperhomocysteinemia is related to 5-year mortality independent of other major risk factors and appears to be a stronger (1.9-fold) risk factor for mortality in type 2 diabetic patients than in nondiabetic subjects.

Part 5: The association of elevated blood levels of homocyst(e)ine with increased cardiovascular mortality.

Blood homocyst(e)ine levels are an important, independent and frequent risk factor for clinical atherosclerosis and venous thrombosis. Folic acid, vitamins B6 and B12, renal and thyroid functions, certain medications and certain genotypes are known to modulate plasma homocyst(e)ine levels. Intake of B vitamins through diet, supplementation and fortified foods effectively reduces homocyst(e)ine concentration and thus may reduce the risk of cardiovascular disease. This is true even in individuals who are genetically predisposed to hyperhomocyst(e)inemia. (Malinow MR Can J Cardiol 1999 Apr;15 Suppl B:31B-34B)

The rare inherited disease homocystinuria with hyper-homocystinaemia is associated with childhood onset of cardiovascular occlusive disease. A milder variant of the disease (heat labile methylene tetra hydrofolate reductase) occurs in 10-15% of some populations and also carries a risk of higher than usual coronary and other vascular occlusive disease. A further common genetic variant of folate metabolism has also been described, with accompanying increased requirement for folic acid in the diet. The high levels of homocyst(e)ine found in the blood of these individuals can usually be lowered by treatment with folic acid or folic acid together with vitamin B12 /and pyridoxine. Such a reduction can alleviate the risk of premature vascular disease if successful lowering of homocyst(e)ine levels can be attained.

Individuals with folic acid deficiency -of even mild degree, also have elevated levels of homocyst(e)ine which can be normalised by folic acid supplementation or food fortification. The commonest group of individuals with folic acid deficiency are the elderly who often have an associated vitamin B12 deficiency. Correction of the folic acid deficiency without pari passu correcting the B12 deficiency may produce adverse neurological effects so it is important to correct both deficiencies simultaneously, quite apart from the additional homocyst(e)ine lowering effects which may result from B12 treatment. There has been described a common variant of B12 metabolism which results in an increased dietary requirement for B12 and may precipitate relative B12 deficiency.

Some forms of homocystinaemia are also corrected by another B group vitamin-pyridoxine.

Furthermore, betaine is capable of reducing plasma homocyst(e)ine in those individuals who have a deficiency of cystathione beta-synthetase activity (Dudman et al J Nutr (US) 1996 126 (4 Suppl) 1295S-1300S)

Thus the most effective way in which high levels of homocyst(e)ine can be lowered is by giving all three vitamins - and perhaps betaine.

Lowering of elevated levels of homocyst(e)ine has been shown to be effective in lowering

345 coronary heart disease risk and possible stroke risk also possibly through the mechanism of reducing vascular resistance and thrombotic tendency. An additional unrelated preventive aspect of such additions may be diminution of the occurrence of the birth defect spina bifida and related neural tube defects if these vitamin supplements are consumed during early pregnancy.

350 VARIATIONS

While this invention provides for foods having compositions as described previously, the invention could also provide a medication according to the above principles, in which the effect of the replacement of type A1 or the B beta casein is mimicked by a composition capable of compensating for the effects of the beta-casomorphin produced from those caseins.

355 Betaine is one example of a compound outside the definition of B vitamins that is useful in controlling elevated levels of homocyst(e)ine and there may be others.

While the daily doses suggested herein are based on the assumption that substantially no other sources of vitamins are available to an "average adult" consumer, there are grounds for reducing the doses if alternative sources are steadily available.

360 COMMERCIAL BENEFITS or ADVANTAGES

Given the high incidence of heart disease together with the difficulty of reliably diagnosing diabetes, and the marginal status of much of the population in relation to folic acid intake requirements, it is evident that this invention could, with little inconvenience in terms of administration and without great difficulty of manufacture, save many of the costs associated
365 with cardiovascular and cerebrovascular (and other) diseases, both in terms of institutional (treatment) costs and personal losses. For example the invention could be marketed as another type of milk, perhaps called "Heart milk" and used like ordinary milk. The additives should be sufficiently heat stable to survive use in tea or coffee.

370 Finally, it will be understood that the scope of this invention as described and/or illustrated within this provisional specification is not limited to the preferred embodiments described herein for illustrative purposes. Those skilled in the art will appreciate that various modifications, additions, and substitutions are possible without departing from the scope and spirit of the invention as set forth.

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Ensor and Associates

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for

New Zealand Milk Institute Limited

ABSTRACT

Fortified dietary formulations are described for the reduction of the incidence and effects of vascular, particularly cardiovascular disease, at least in cases where raised plasma homocyst(e)ine and verified, forecasted, or unverified diabetes is involved in the aetiology. The formulations minimise arterial wall pathology, resulting vascular impairment by (a) providing adequate B vitamins (pyridoxine, cyanocobalamine, and folic acid), and (b) by providing milk with low or absent caseins of the types liable to produce beta-casomorphines on partial digestion, that is, retaining type A2 and discarding type A1 and B casein. Practical fortified diets include treated, selected milks, and selected milks together with treated cereals.

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